Exhibit C

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Limitations and Strengths of Spontaneous Reports Data*

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ABSTRACT

US Food and Drug Administration (FDA) monitoring of the continued safety of marketed medical products depends greatly on spontaneous reporting of serious adverse events by health professionals. Despite its inherent limitations, the national postmarketing surveillance system provides vital information of clinical importance. ***Key words***: FDA, spontaneous reports, postmarketing surveillance, adverse drug event.

INTRODUCTION

As with clinical trials, there are important limitations to consider when using spontaneously reported adverse event information. These limitations include difficulties with adverse event recognition, underreporting, biases, estimation of population exposure, and report quality. This paper addresses the limitations and strengths of data obtained from spontaneous reporting of adverse events.

LIMITATIONS OF SPONTANEOUS REPORTS DATA

Adverse Event Recognition

The recognition of adverse drug events, or any other medical product-associated adverse event, is quite subjective and imprecise.[1] Although an attribution between the medical product and the observed event is assumed with all spontaneously reported events, every effort is made to rule out other explanations for the event in question. It is well known that placebos[2] and even no treatment[3] can be associated with adverse events. In addition, an underlying background rate almost always exists for any clinical event in a population, regardless of whether exposure to a medical product occurred.

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Reaching a firm conclusion about the relationship between exposure to a medical product and the occurrence of an adverse event can be difficult. In one study, clinical pharmacologists and treating physicians showed complete agreement less than half the time when determining whether medication, alcohol, or "recreational" drug use had caused hospitalization.[4]

Such considerations emphasize the crucial need for careful, thoughtful review of adverse event reports on their receipt by the US Food and Drug Administration (FDA) or the manufacturer. It is through this process that causality, or at least a high degree of suspicion for a product-adverse event association, is put to the test.

Underreporting

Another major concern with any spontaneous reporting system is underreporting of adverse events.[5–8] It has been estimated that rarely more than 10% of serious adverse drug reactions (ADRs), and 2% to 4% of nonserious reactions, are reported to the British spontaneous reporting program.[6] A similar estimate is that the FDA receives by direct report less than 1% of suspected serious ADRs.[8] This means that cases reported spontaneously to any surveillance program, which comprise the numerator, generally represent only a small portion of the number that have actually occurred. The effect of underreporting can be somewhat lessened if submitted reports, irrespective of number, are of high quality.

Biases

Unlike clinical trial data, which are obtained under strictly controlled conditions, spontaneously reported information is uncontrolled and therefore subject to the possible influence of a number of biases that can affect reporting. These biases include the length of time a product has been on the market, country, reporting environment, detailing time, and quality of the data.[9] A striking illustration of the impact that one such factor can have is the finding that the peak of spontaneous ADR reporting for a drug is at the end of the second year of marketing, with a subsequent precipitous decline in reporting[10] despite a lack of apparent decline in usage or change in ADR incidence.[10,9] In addition to these biases, it is possible that reported cases might differ from nonreported cases in characteristics such as time to onset or severity.[11]

Estimation of Population Exposure

Compounding these numerator limitations is the lack of denominator data, such as user population and drug exposure patterns.[11] These data would provide the exact number of patients exposed to the medical product and thus at risk for the adverse event of interest. Numerator and denominator limitations make incidence rates computed from spontaneously reported data problematic,[11] if not completely baseless. However, even if the precise number of exposed patients is not known, estimation of the exposure can be attempted by using drug utilization data.[12]

This approach, whose basic methodologies are applicable to medical products in general, can be of great use. Major sources of data on the use of drugs by a defined population include market surveys based on sales or prescription data, third-party payers or health maintenance organizations, institutional/ambulatory settings, or specific pharmacoepidemiologic studies.[12] Cooperative agreements

and contracts with outside researchers enable the FDA to use such databases in its investigations. Device utilization studies use the same sources of data, as well as Medicare-derived information.

Care must be taken in interpreting results from studies using these databases. That drug prescribing does not necessarily equal drug usage,[12] and whether results derived from a specific population (such as Medicaid recipients) are applicable to the population at large, need to be weighed carefully.

Report Quality

The ability to assess, analyze, and act on safety issues based on spontaneous reporting is dependent on the quality of information submitted by health professionals in their reports. A complete adverse event report should include the following: product name (and information such as model and serial numbers in the case of medical devices); demographic data; succinct clinical description of adverse event, including confirmatory/relevant test/laboratory results; confounding factors (eg, concomitant medical products and medical history); temporal information, including date of event onset and start/stop dates for use of medical product; dose/frequency of use (as applicable); biopsy/autopsy results (as applicable); dechallenge/rechallenge information (if available); and outcome.

STRENGTHS OF SPONTANEOUS REPORTS DATA

Large-Scale and Cost-Effective

Two vital advantages of surveillance systems based on spontaneous reports are that they potentially maintain ongoing surveillance of all patients and are relatively inexpensive.[13] In fact, they are probably the most cost-effective way to detect rare, serious adverse events not discovered during clinical trials.

Generation of Hypotheses and Signals

Making the best possible use of the data obtained through monitoring underlies postmarketing surveillance.[14] Toward that goal, the great utility of spontaneous reports lies in hypothesis generation,[7] with the need to explore possible explanations for the adverse event in question. By fostering suspicions,[15] spontaneous report-based surveillance programs perform an important function, which is to generate signals of potential problems that warrant further investigation.

Assessment of the medical product-adverse event relationship for a particular report or series of reports can be difficult. The table lists factors that are helpful in evaluating the strength of association between a drug and a reported adverse event.[16]

The stronger the drug-event relationship in each case and the lower the incidence of the adverse event occurring spontaneously, the fewer case reports are needed to perceive causality.[17] It has been found that for rare events, coincidental drug-event associations are so unlikely that they merit little concern, with greater than three reports constituting a signal requiring further study.[11] In fact, it has been suggested that a temporal relationship between medical product and adverse event, coupled with positive dechallenge and rechallenge, can make isolated reports conclusive as to a product-event association.[18] Biologic plausibility and reasonable strength of association aid in deeming any association as causal.[6] However,

Table. Useful factors for assessing causal relationship between a drug and a reported adverse event.[16]

Chronology of administration of agent, including beginning and ending of treatment and adverse event onset
Course of adverse event when suspected agent stopped (dechallenge) or continued
Etiologic roles of agents and diseases in regard to adverse event
Response to readministration (rechallenge) of agent
Laboratory test results
Previously known toxicity of agent

achieving certain proof of causality through postmarketing surveillance is unusual.[17] Attaining a prominent degree of suspicion is much more likely, and may be considered a sufficient basis for regulatory decisions.[17]

Clinician Contribution

The reliance of postmarketing surveillance systems on health professional reporting enables an individual to help improve public health. One study showed that direct practitioner participation in the FDA spontaneous reporting system was the most effective source of new ADR reports that led to changes in product labeling.[19] Postmarketing surveillance is further enhanced by ensuring that the information provided in the adverse event report is as complete and in depth as possible.

CONCLUSIONS

Although possessing inherent limitations, postmarketing surveillance based on spontaneous reports data is a powerful tool for detecting adverse event signals of direct clinical impact. It is dependent not only on health professional participation, but also on the quality of the reports submitted.

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